

Effectiveness of aflibercept treatment after dexamethasone in macular edema caused by branch retinal vein occlusion: Case series

Branch retinal vein occlusion dexamethasone, aflibercept

Tayfun Şahin
Department of Ophthalmology, Hitit University Medicine Faculty, Corum, Turkey

Abstract

Aim: This study aims to assess the effectiveness of aflibercept in patients with macular edema caused by Branch Retinal Vein Occlusion following dexamethasone implant treatment.

Material and Methods: This study included treatment-naive 20 eyes of 20 patients. At baseline and follow-ups, the patients' Best Corrected Visual Acuity, the Central Macular Thickness and Central Macular Volume measures taken with Spectral-Domain Optical Coherence Tomography were recorded. The patients who had deterioration of visual acuity or macular thickness ≥ 300 were administered intraocular injection again. Recurrent cases following dexamethasone injection were administered aflibercept injection three times with an interval of one month.

Results: Compared to the baseline, the patients demonstrated an increase in visual acuity and a decrease in macular thickness and macular volume following the dexamethasone injection ($p=0.013$, $p=0.009$, $p=0.021$, respectively). In an average of three and half months after the injection, there was a decrease in visual acuity (0.90 ± 0.44 logMAR), an increase in macular thickness (579 ± 107 μm) and macular volume (12.25 ± 1.55 mm^3) ($p>0.05$ all). Three months after the the completion of three aflibercept injections, there was no deterioration in visual acuity (0.41 ± 0.23 logMAR) according to the recurrence time of macula edema ($p=0.048$). Macular thickness (288 ± 47 μm) and macular volume (8.59 ± 0.96 mm^3) values demonstrated nonsignificant increases ($p>0.05$).

Discussion: Aflibercept treatment is effective in recurrence following the Dexamethasone treatment in macula edema caused by branch retinal vein occlusion.

Keywords

Aflibercept; Combination treatment; Dexamethasone; Macular edema; Vein occlusion

DOI: 10.4328/ACAM.20371 Received: 2020-10-11 Accepted: 2020-11-18 Published Online: 2020-11-26 Printed: 2021-06-01 Ann Clin Anal Med 2021;12(6):642-646

Corresponding Author: Tayfun Şahin, Hitit University Medicine Faculty, Department Of Ophthalmology, 019030 Corum, Turkey.

E-mail: drtayfunsahin82@gmail.com P: +90 506 328 4338 F: +90 364 713 0101

Corresponding Author ORCID ID: <https://orcid.org/0000-0003-2319-0807>

Introduction

Retinal venous occlusion (RVO) is the most common retinal vascular disease that causes vision loss after diabetic retinopathy [1]. The most common cause of RVO is the hemodynamic impairment in the veins associated with the compression caused by the atherosclerotic changes in the retinal artery [2]. Macular edema is the most common cause of vision loss in non-ischemic RVO [3]. Vascular permeability increases due to the increased mediators in the environment due to inflammation in RVO, which leads to macular edema [4]. The inhibition of the vascular endothelial growth factor (VEGF) in the RVO-associated macular edema could enable to decrease macular edema and increase vision [5]. Other inflammatory mediators and cytokines apart from VEGF also contribute to macular edema in RVO [6]. Targeting this increased cytokine and mediators in the treatment could yield more successful results in reducing macular edema. Corticosteroids inhibit the synthesis of other inflammatory cytokines and inflammatory cell migration. In addition, corticosteroids are known to cause cataract and increase intraocular pressure [7]. In cases with RVO-associated macular edema, the primary stage treatment generally includes anti-VEGF agents to avoid the potential side effects of corticosteroids.

In this study, we aimed to show the efficiency of the aflibercept treatment in cases with RVO-associated macular edema that developed recurrence following a dexamethasone implant treatment.

Material and Methods

This retrospective study was conducted from September 2017 to October 2018 and involved 20 eyes of 20 patients who applied to the ophthalmic clinic of our hospital due to macular edema caused by branch retinal vein occlusion (BRVO) and did not have any treatments before. Ethics committee approval was obtained (2019-31 decision number dated 10.07.2019) from the university, and the study followed the principles of the Declarations of Helsinki. A written informed consent form was obtained from the patients.

The patients underwent full ophthalmological examinations including baseline and follow-up best-corrected visual acuity (BCVA) measured with Snellen chart, biomicroscopic examination findings, intraocular pressure measurements (measured with Goldmann) and dilated fundus findings. Central macular thickness (CMT) and central macular volume (CMV) measurements were performed with Spectral-Domain Optical Coherence Tomography (SD-OCT; Heidelberg Engineering, Heidelberg, Germany). Visual acuity taken with Snellen was converted to logMAR. Fluorescein Fundus Angiography (FFA) of the patients was performed during the first application. Cases with suspected neovascularization in fundus during follow-ups received FFA again.

Intraocular injections were performed in an operating room environment. Topical anesthesia was administered with 0.5% proparacaine (Alcaine; Alcon Laboratories). The area around the eye was cleaned with 10% povidone-iodine. Povidone-iodine (5%) was administered intraocularly, and at least three minutes last while waiting for antisepsis. The area around the eye was covered with a sterile drape, and an eyelid speculum

was placed. The patients' intravitreal injections were done posterior to the superotemporal limbus (4 mm in phakic, 3.5 mm in pseudophakia).

In the beginning, the patients were administered 0.7 mg dexamethasone (Ozurdex; Allergan, Inc., Irvine, California, USA) implant injection. The patients' follow-ups were performed in the second week, the fourth week, and then once a month after the dexamethasone injections. During their follow-ups, the patients who were found to have a one-level decrease in vision or a macular thickness of $\geq 300 \mu\text{m}$ were accepted to have developed recurrence. The patients who were accepted to have recurrence were administered intravitreal aflibercept (Eylea VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Bayer Health-Care Pharmaceuticals, Berlin, Germany, 2.0 mg) injections three times with an interval of one month. After the three aflibercept injections, the patients were followed up once a month. The patients who were found to have a one-level decrease in vision or a macular thickness of $\geq 300 \mu\text{m}$ after the administration of three injections of aflibercept were applied aflibercept once as a maintenance treatment.

The patients who were administered an intravitreal injection, who received laser in the retina, who underwent vitrectomy surgery, who had a retina pathology apart from venous occlusion (diabetic retinopathy, choroidal neovascularization) and glaucoma were excluded from the study.

Statistical Method

Statistical analyses of the data were performed using SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA, License). In line with the data distribution, descriptive statistics were reported as mean \pm standard deviation or median (minimum-maximum). Descriptive statistics of the categorical data were presented as numbers and percentages (%). Normality distribution of the categorical data was presented as numbers and percentages (%). The normality distribution for the statistical test choice was evaluated with the Shapiro-Wilk Test. Repeated measure comparisons were performed using Repeated Measures ANOVA when the data were normally distributed and Friedman's Test for the non-parametric data when the data were not normally distributed. AVONA and Friedman test and Bonferroni corrected posthoc multiple comparison tests were utilized to identify different measurements. Statistical significance was taken as $p < 0.05$.

Results

This study involved 20 patients with BRVO-associated macular edema.

The demographic characteristics of the patients are demonstrated in Table 1.

BCVA was found to demonstrate an increase compared to the baseline (1.30 ± 0.59 logMAR) in the first month following the dexamethasone injection (0.79 ± 0.42 logMAR) ($p = 0.013$). Follow-up examinations showed that recurrence occurred in four patients (20%) in the third month, 12 patients (60%) in the fourth month, and four patients (20%) in the fifth month. Although BCVA was better than baseline (0.90 ± 0.44 logMAR) when macular edema recurred, the difference was not statistically significant ($p > 0.05$). Although CMT ($579 \pm 107 \mu\text{m}$) and CMV ($12.25 \pm 1.55 \text{ mm}^3$) values were also better

than baseline, these values were not statistically significant ($p>0.05$). After the three aflibercept injections administered with an intervals of one month, there was an increase in BCVA (0.47 ± 0.36 logMAR), and a decrease in CMT (265 ± 43 μ m) and CMV (8.35 ± 0.79 mm³) values ($p=0.002$, $p=0.001$, $p=0.001$, respectively). Compared to the time of recurrence three months after the last aflibercept injection, no worsening was reported in BCVA (0.41 ± 0.23 logMAR) ($p=0.048$), and CMT (288 ± 47 μ m) and CMV (8.59 ± 0.96 mm³) were found to have non-significant increases ($p>0.05$). (Figure 1) (Table 2).

Table 1. Demographic characteristics of the patients

Age (mean \pm sd)	63 \pm 7.71 years
Gender (male / female)	12 / 8
Lens status (phakic / pseudophakic)	16 / 4
Baseline macular thickness (μ m) (mean \pm sd)	742 \pm 159
Baseline macular volume (mm ³) (mean \pm sd)	14.72 \pm 2.43
Sd: Standard deviation	

Table 2. Changes of BCVA, CMT and CMV

	Baseline	DEX after 1 month	DEX after 3 months	DEX after recurrence	AFL after 1 month	AFL after 3 months
BCVA (logMAR)	1.30 \pm 0.59	0.79 \pm 0.42	0.89 \pm 0.51	0.90 \pm 0.44	0.47 \pm 0.36	0.41 \pm 0.23
CMT (μ m)	743 \pm 160	369 \pm 130	464 \pm 213	579 \pm 107	265 \pm 43	288 \pm 47
CMV (mm ³)	14.72 \pm 2.43	10.00 \pm 2.18	10.98 \pm 2.34	12.25 \pm 1.55	8.35 \pm 0.79	8.59 \pm 0.96

BCVA: Best corrected visual acuity, CMT: Central macular thickness, CMV: Central macular volume, logMAR: log of the Minimum Angle of Resolution, DEX: Dexamethasone, AFL: Aflibercept

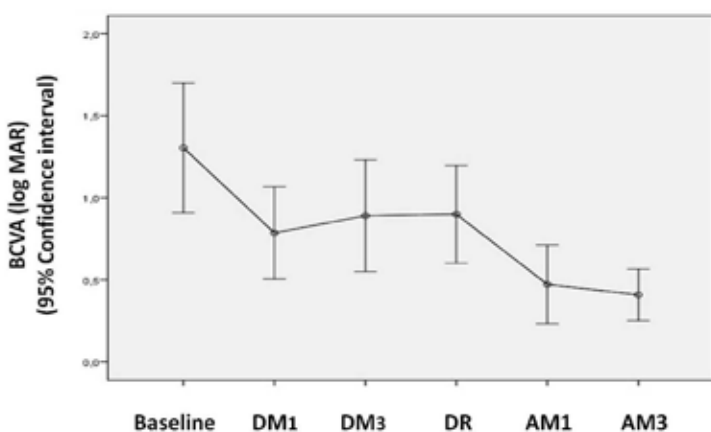


Figure 1. The change of visual acuity (logMAR)
BCVA: Best corrected visual acuity, logMAR: log of the Minimum Angle of Resolution, DM1: Dexamethasone after 1 month, DM3: Dexamethasone after 3 month, DR: Dexamethasone after recurrence, AM1: Aflibercept after 1 month, AM3: Aflibercept after 3 months

It was considered that the patients did not need treatment (a one-level decrease in vision or a macular thickness of over 300 μ m) up to six months after the third aflibercept injection. In the sixth month, four patients (20%) needed to be administered aflibercept injection. The other patients did not need treatment. Two months after the dexamethasone implantation, four patients (20%) had intraocular pressure (IOP) of over 21 mmHg. With a two-month topical antiglocomatose treatment, the IOP of these patients was taken under control. At the end of the first year, four patients were found to have cataract, and four patients (20%) were found to have neovascularization in the retina.

Discussion

To the best of our knowledge, the present study is the first study that assessed the efficiency of aflibercept after dexamethasone in cases with BRVO-associated macular edema.

After the dexamethasone injection, the increase in BCVA and the decrease in CMT and CMV were found to last throughout three-and-half months on average. At the end of this period, BCVA worsened and CMT and CMV values became close to baseline values.

In RVO, hypoxic pathophysiologic cascades associated with impaired hemodynamics are involved or a local inflammatory process starts. In vitreous, there is an increase in the number of inflammatory mediators and free radicals such as interleukin 6-8, monocyte chemoattractant protein-1, angiotensin II, prostaglandins, and VEGF. The inner blood-retinal barrier connected to these mediators deteriorates and leakage occurs, which develops macular edema resulting in vision loss. Therefore, targeting other inflammatory mediators along with VEGF in the treatment of the RVO-associated macular edema is of importance in the treatment. Dexamethasone has been reported to decrease edema in the inflammatory response, fibrin accumulation, capillary leakage, inhibit phagocytic migration, and suppress inflammation. VEGF is a strong stimulus for vascular permeability. Corticosteroids have been shown to inhibit VEGF expression [6].

GENEVA study showed that dexamethasone implant was efficient in the treatment of cases that had RVO-associated macular edema. Patients who were administered dexamethasone injection were found to have increased visual acuity and decreased macular thickness compared to the patients who were administered a sham injection. The study reported that dexamethasone efficiency reached the maximum level in the second month, and it could continue up to 180 days [8]. Studies conducted later reported that the efficiency lasted three months on average and could degradedly continue up to six months [9, 10]. Joshi et al. treated patients who had RVO-associated macular edema and who developed recurrent macular edema after the dexamethasone implant treatment for the second time. They found that the duration of the efficiency was shortened in repeated dexamethasone injections [11]. In their study on the patients with RVO-associated macular edema, Yücel et al. reported that treatment with dexamethasone implant enabled an anatomic recovery rather than a functional recovery [12]. GENEVA study also evaluated the patients who

were administered dexamethasone in terms of the side effects as well. The study showed that 16% of the patients had an IOP level of over 25mmHg, and 7.3% developed cataract [8].

In this study, the cases that developed recurrence after the dexamethasone treatment were given treatment by shifting to aflibercept. Such a shift was done as it is known that dexamethasone could cause cataracts, increase IOP, and shorten the duration of the efficiency of repeated injections [7, 11]. When macular edema developed recurrence, aflibercept, an anti-VEGF agent with combined effect, was utilized in the treatment. Aflibercept connects and deactivates the placental growth factor (PGF) that plays an important role in VEGF-A, VEGF-B, and vein permeability. After receiving three aflibercept injections, the patients in this study had no visual impairment three months later; however, CMT and CMV were found to have non-significant increases.

Due to the high affinity of aflibercept, it is known to have long-term effects at low concentrations [13]. The COPERNICUS and GALILEO studies have also reported that aflibercept was efficient in RVO-associated macular edema [14, 15]. VIBRANT evaluated whether aflibercept was more efficient compared to grid laser in BRVO-associated macular edema cases. It was reported that the eyes administered aflibercept showed significant recovery in their vision levels and a decrease in macular thickness in comparison to the eyes that were administered a grid laser [16]. It was reported that as aflibercept molecule regulated retinal microcirculation, it could provide an increase in vision [12].

Herbaut et al. reported that cases with diabetic macular edema with no response to dexamethasone or ranibizumab treatment were administered treatment by exchanging with aflibercept. After the treatment, 60% of the patients had a decrease in CMT and recovery of visual acuity [17]. Chiquet et al. continued treatment with dexamethasone in cases that had RVO-associated macular edema and who did not respond to bevacizumab treatment. In the first month, the patients were reported to have improved vision and decreased CMT (this effect worsened until the 12th month). In the same study, eight cases without any response to dexamethasone were administered bevacizumab treatment. In this group, no changes were reported in visual acuity, and the decrease in CMT was reported only in the first month [18]. The study conducted by Chiquet et al. was similar to the present study as they administered anti-VEGF (bevacizumab) following dexamethasone. The patients in this study were treated with aflibercept after dexamethasone. The patients were found to have improved vision and decreased CMT and CMV. After the third aflibercept injection, the efficiency of the treatment took about six months. After six months, four patients needed to be administered aflibercept injection once. The rest of the patients did not need any treatment.

Lu et al. reported that the combination of anti-VEGF and dexamethasone treatment was found to have better results compared to dexamethasone monotherapy in cases with RVO-associated macular edema [19]. We think that after the strong inhibition of mediators and cytokines released in the environment with dexamethasone in the beginning, regulation of retinal microcirculation leads to successful outcomes with aflibercept that deactivates VEGF-A, VEGF-B and PGF in

patients with BRVO-associated macular edema. We believe that this combination could be an effective treatment option.

This study has a number of limitations. Firstly, we did not have a control group. When we conducted this study, Social Security Institution recommended and paid the dexamethasone implant treatment in patients with RVO-associated macular edema. Therefore, we did not form a control group and started the treatment of the patients initially with the dexamethasone implant. The second limitation was that we had a limited number of patients. Most of the patients who applied to our clinic were patients who have previously been treated (intravitreal treatment/laser treatment). A higher number of patients and the formation of a control group (aflibercept monotherapy group) could be beneficial for future studies

Conclusion

The aflibercept combination treatment after dexamethasone gives anatomically and functionally positive results in BRVO-associated macular edema. We think that this treatment combination could decrease the total number of intravitreal injections to be administered to the patient. Future studies could shed more light on the issue.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Ho M, Liu DT, Lam DS, Jonas JB. Retinal vein occlusions, from basics to the latest treatment. *Retina*. 2016;36(3):432–48.
2. Lahey JM, Kearney JJ, Tunc M. Hypercoagulable states and central retinal vein occlusion. *Curr Opin Pulm Med*. 2003;9(5):385–92.
3. Wong TY, Scott IU. *Clinicalpractice*. Retinal-vein occlusion. *N Engl J Med*. 2010;363(22):2135–44.
4. Campochiaro PA, Bhisitkul RB, Shapiro H, Rubio RG. Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion. *Ophthalmology*. 2013;120(4):795–802.
5. Varma R, Bressler NM, Sun T, Lee P, Dolan CM, Ward J, et al. Improved vision-related function after ranibizumab for macular edema after retinal vein occlusion: results from the BRAVO and CRUISE trials. *Ophthalmology*. 2012;119(10):2108–18.
6. Yoshimura T, Sonoda KH, Sugahara M, Mochizuki Y, Enaida H, Oshima Y, et al. Comprehensive analysis of inflammatory immune mediators in vitreoretinal diseases. *PLoS One*. 2009;4(12):e8158.
7. Ashraf M, Souka AAR. Steroids in central retinal vein occlusion: is there a role in current treatment practice?. *J Ophthalmol*. 2015;2015:594615.
8. Haller JA, Bandello F, Belfort R, Blumenkranz MS, Gillies M, Heier J, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion. Twelve-month study results. *Ozurdex GENEVA Study Group*. *Ophthalmology*. 2011;118(12):2453–60.
9. Manousaridis K, Peter S, Mennel S. Outcome of intravitreal dexamethasone implant for the treatment of ranibizumab-resistant macular edema secondary to retinal vein occlusion. *Int Ophthalmol*. 2017;37(1):47–53.
10. Michalska-Matecka K, Gaborek A, Nowak M, Halat T, Pawłowska M, Śpiwak D. Evaluation of the effectiveness and safety of glucocorticoids intravitreal implant therapy in macular edema due to retinal vein occlusion. *Clin Interv Aging*. 2016;11:699–705.
11. Joshi L, Yaganti S, Gemenetzi M, Lightman S, Lindfield D, Liolios V, et al. Dexamethasone implants in retinal vein occlusion: 12-month clinical effectiveness using repeat injections as-needed. *Br J Ophthalmol*. 2013;97(8):1040–4.

12. Yucel OE, Birinci H, Sullu Y. The short-term efficacy of intravitreal ranibizumab, aflibercept and dexamethasone implant in the treatment of macular edema due to non-ischemic central retinal vein occlusion. *Int Ophthalmol*. 2019;39(4):891-901.
13. Holash J, Davis S, Papadopoulos N, Croll SD, Ho L, Russell M, et al. VEGF-Trap: a VEGF blocker with potent anti-tumor effects. *Proc Natl Acad Sci USA*. 2002;99(17):11393-8.
14. Boyer D, Heier J, Brown DM, Clark WL, Vitti R, Berliner AJ, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024-32.
15. Holz FG, Roeder J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, et al. VEGF Trap-Eye for macular edema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol*. 2013;97(3):278-284.
16. Campochiaro PA, Clark WL, Boyer DS, Heier J, Brown DM, Vitti R, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122(3):538-44.
17. Herbaut A, Fajnkuchen F, Qu-Knafo L, Nghiem-Buffet S, Bodaghi B, Giocanti-Auregan A. Switching to Aflibercept in Diabetic Macular Edema Not Responding to Ranibizumab and/or Intravitreal Dexamethasone Implant. *J Ophthalmol*. 2017;2017:8035013.
18. Chiquet C, Bron AM, Straub M, Nghiem-Buffet S, Bodaghi B, Giocanti-Auregan A. Retinal vein occlusions: therapeutic switch in macular edema treatment with a 12-month follow-up. *Ophthalmic Res*. 2016;55(3):152-8.
19. Iu LP, Zhao P, Yeung IY, Fung NS, Lee JW, Wong RL, et al. Sequential therapy with ranibizumab and dexamethasone intravitreal implant is better than dexamethasone monotherapy for macular edema due to retinal vein occlusion. *Br J Ophthalmol*. 2015;99(2):210-4.

How to cite this article:

Tayfun Şahin. Effectiveness of aflibercept treatment after dexamethasone in macular edema caused by branch retinal vein occlusion: Case series. *Ann Clin Anal Med* 2021;12(6):642-646